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REVIEW ARTICLE

Decrease of Salivary Melatonin Level in Periodontal Disease: A Review Article

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Abstract

Background: Melatonin is a circulating hormone that is mainly released from the pineal gland. It possesses antioxidant, free-radical scavenging, and immune-enhancing properties. A growing number of studies reveal a complex role for melatonin in influencing various diseases, including periodontal diseases. The purpose of this strudy literature was to knowing the possible relations between salivary melatonin levels and periodontal diseases. **Objective:** the aim of this study is to find the correlation of salivary melatonin level in periodontal disease.

Discussion: The mean of salivary melatonin level was significantly lower in patients with periodontitis compared to healthy subjects. Salivary melatonin concentration decreased in periodontitis patients. Based on the results of any study, it can probably be concluded that salivary level of melatonin has an important role in the pathogenesis of periodontal diseases. It is also worth knowing that this factor could probably be used as a pivotal biological marker in the diagnosis and possible treatment of these diseases, although further research is required to validate this hypothesis. **Conclusion:** The salivary melatonin level can be used as the biological marker in the early diagnosis of periodontal disease. Keywords: melatonin level, pineal gland, periodontal disease, saliva

1 | INTRODUCTION

Melatonin is the main secretion product from the pineal gland whose role is to destroy free radical. Melatonin is also immunomodulator and antioxidant that play a role in the inflammatory process and cell damage caused by toxic oxygen derivatives. Melatonin plays a role in the proliferation of collagen and bone tissue. In addition, this hormone acts as a protector against cellular degeneration associated with aging and exposure to toxins. Several studies suggest that melatonin plays

a role in influencing several diseases, including periodontal disease. Periodontal disease is a dental and oral health problem that has a fairly high prevalence in society with the prevalence of periodontal disease in all age groups in Indonesia is 96.58%. Periodontal disease is a disease in the oral cavity that affects almost all humans in the world and reaches 50% of the total adult population.[1]

Periodontal disease is a lesion of the oral cavity that causes the tooth supporting area to lose its collagen structure, and is a response to the accumulation of bacteria in the periodontal tissue. If this periodontal disease is not treated properly, it can cause tooth loss. The accumulation of bacterial plaque on the tooth surface is a major cause of periodontal disease. Plaque contains more than 500 species of bacteria. Therefore, periodontal disease is a disease that is difficult to prevent and treat. Based on the background described above, the purpose of this paper is to determine the relationship between decreased salivary melatonin levels and periodontal disease. (1) , (2)

2 | MELATONIN HORMONE

Melatonin (N-acetyl-5-methoxytryptamine) is a hormone that is synthesized by the pineal gland. The mechanism of melatonin synthesis is initiated from pinealocytes, melatonin will be synthesized by pinealocytes then will carry free tryptophan from the blood and convert it into serotonin, which involves the enzymes tryptophan-5-hydroxylase and 5-hydroxytryptophan decarboxylase, respectively, hydroxylate and decarboxylation of tryptophan respectively. At night, serotonin is converted to N-acetylserotonin by the action of N-acetyltransferase. After that the hydroxyindole-O-methyl transferase enzyme acts on N-acetylserotonin causing methylation and then forming melatonin.[2]

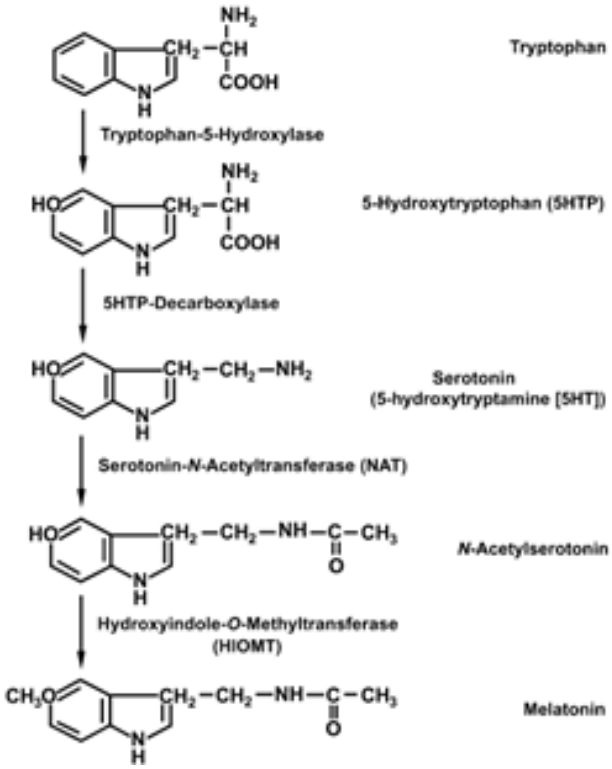

FIGURE 1: ChemistyStructure of Melatonin Synthesis from Tripofan.[3]

Melatonin which is also called the ”hormone of darkness” has several physiological functions in the body, including controlling circadian rhythm, regulating body temperature, activating the immune system, controlling the secretion of growth hormone and Adrenocortico Hormone, increasing osteoblast differentiation in vitro and increasing in vivo formation. and has a hypnotic action for sleep initiation as an activator to open the ”sleep gate”. (3) , (4) In addition to these functions, melatonin has several other roles in the body, one of the proven roles of melatonin in the body, namely as a carrier for free radicals from the body which are then removed from the body or in other words, melatonin acts as an antioxidant produced from the body. In addition, melatonin is also able to influence the presence of oxidative stress indirectly by stabilizing the inner mitochondrial membrane and increasing its electron transport chain. Melatonin stimulates a number of antioxidant enzymes, including superoxide dismutase, glutathione peroxidase, glutathione reductase,

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and catalase. Another role of melatonin in the body is as an immunomodulator by regulating the secretion of interleukin-2 (IL-2), interferon-a (INF-a), the consequent activation of CD4 + lymphocytes and can also stimulate the proliferation and synthesis of type I collagen. (5)

Increase of Melatonin Level

Melatonin levels in the body increase when a person sleeps at night. In dark light conditions, the neural electrical signals that have been received by the central nervous system will be transmitted to the pineal gland and will release norepinephrine which will initiate melatonin synthesis. The pineal gland which produces the hormone melatonin is a gland that is very sensitive to light, so this gland is active at night. Based on research, it turns out that in normal people, this metallonin hormone has increased production around 02.00-04.00 at night so that at that time the body's melatonin levels reach a maximum. (6)

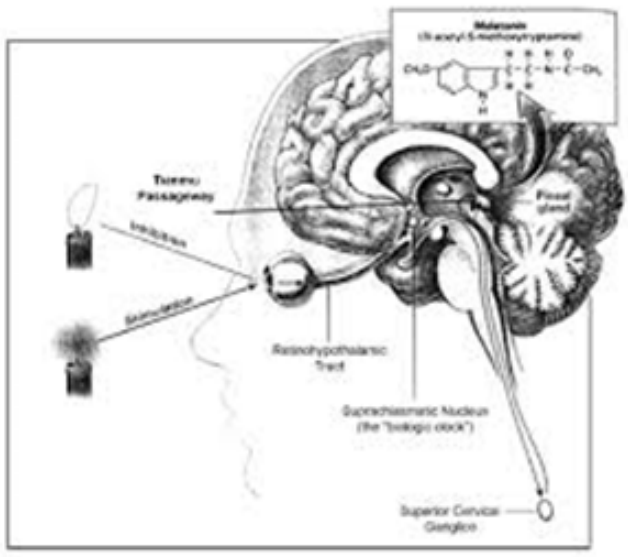

FIGURE 2: Effect of light in melatonin secretion.

Decrease of Melatonin Level

Based on the function of melatonin, melatonin levels in the body can decrease if there is inflammation in the body, increased free radicals, bone damage, immune system disorders, oxidative stress and circadian rhythm disorders. (7) If the circadian rhythm is disturbed, the production of the hormone melatonin will be disrupted due to the pineal gland unable to produce melatonin due to the presence of light. In addition, the presence of inflammation and free radicals in the body simultaneously can cause the body to require high levels of melatonin so that the melatonin in the body decreases continuously. (8)

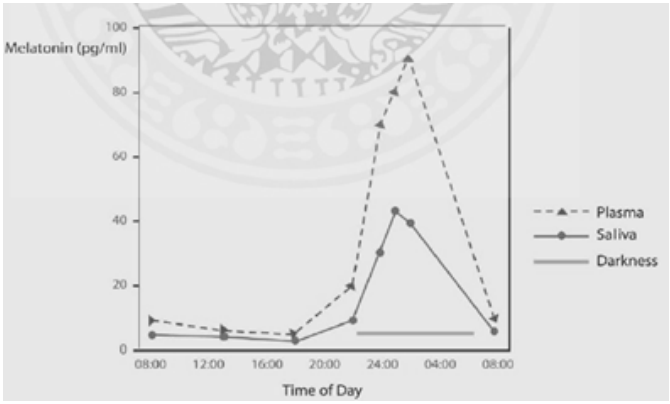

FIGURE 3: Melatonin level during 24 hours period.

Periodantal Disease

Periodontal disease is a disease that occurs in the mouth. This disease is characterized by inflammation of the periodontium tissue which can then affect the periodontal ligament and alveolar bone. The periodontium tissue is the tissue found in the mouth consisting of gingiva, cementum, alveolar bone, and periodontal ligament. Periodontal disease is caused by the accumulation of bacteria that adhere to the surface of the teeth, especially in the area under the gingiva. Subgingival bacteria colonize to form periodontal pockets and cause further inflammation of the gingival tissue, and in advanced periodontal disease progressive alveolar bone loss occurs and if treatment is not performed it will result in tooth loss. Gingival inflammation, bacterial infection, alveolar bone damage, and subsequent tooth loss are processes of periodontal disease. (9)

Histopathology of Periodontal Tissue

The pathogenesis of periodontal disease begins with early gingivitis, advanced gingivitis and if there is continuous inflammation it can cause periodontitis. The periodontal tissue structure when inflamed is first seen around the small gingival vessels, apical to the epithelium jungtion. The early signs of early gingivitis are plaque deposits, the initial inflammatory changes will continue with increased gingival fluid flow and PMN migration. Changes that occur in both the junction epithelium and the cravicular epithelium

are a sign of cell separation and some of the proliferation of basal cells. The interdental papillae become redder and swollen and bleed easily. (10)

Furthermore, advanced gingivitis occurs within 2-3 weeks, will form gingivitis that is even more severe. At this stage mast cells are also found. Immunoglobulins, especially IgG are found in the epithelium and connective tissue. The gingiva is red, swollen and bleeds easily. With worsening collagen breakdown and inflammatory swelling, the gingival margins can easily be removed from the tooth surface, increasing the likelihood of a gingival pocket or false pocket being identified. At this stage there has been degeneration of the epithelial cells of the junction and some have proliferated from the basal layer to the connective tissue below, but at this stage there has not been any migration of epithelial cells in large numbers to the root surface. If the inflammation has spread along the transeptal fibers, it will be seen that there is resorption of the alveolar bone crest. This absorption is reversible, especially in the recovery of inflammation. (11)

One important sign of this disease is the absence of bacteria in the epithelium or connective tissue because the fibrous tissue is damaged in the area around the inflammation, in some areas some distance from the area of inflammation, it is seen that there is proliferation of fibrous tissue and the formation of new blood vessels. This productive restorative activity is a very important characteristic of chronic lesions and, in conditions of long-term irritation and inflammation, fibrous tissue elements will be a major component of tissue transformation. So, damage and repair could take place alternately. If the inflammation is dominant, the tissue will be red, soft and bleed easily, but if the production of fibrous tissue is dominant, the gingival will become hard and pink even though the swelling is less bleeding, or even absent. (9)

Furthermore, periodontitis occurs and is character-ized by plaque irritation and continuous inflamma-tion, the integrity of the epithelium jungtion will be further damaged. Epithelial cells will degenarate and separate, the attachment to the tooth surface will be released. At the same time, epithelium junction will proliferate into the connective tissue and downward on the root surface if the dentogingival and apex fibers of the alveolar bone are damaged. The apical migration of epithelium junction will continue and this epithelium will detach from the tooth surface, forming a periodontal pocket or original pocket. This state is an irreversible change. If a periodontal pocket has formed, the plaque is in contact with cementum. (12)

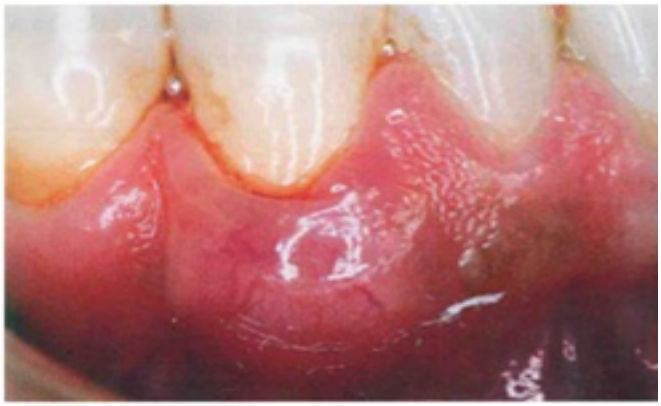

FIGURE 4: Inflamaation inPeriodontal Tissue.

The epithelium of the pocket wall may remain intact or ulcerated. Tissue fluid flow and immigration from PMN will continue and presumably this tissue fluid flow helps to increase subgingival calculus deposition. Spread of inflammation to the crest of the alveolar bone. Characterized by the infiltration of cells into the trabecular spaces, areas of bone resorption and an increase in the size of the trabecular space. There is a tendency for bone resorption to be offset by deposition further away from the inflammatory site. So that the bones will experience remodeling, but still experience damage. Bone resorption starts from the interproximal area to become wide, for example between molar teeth and then if the resorption process continues, the resorption will extend laterally, so that all areas of the alveolar bone crest will be resorbed. (12)

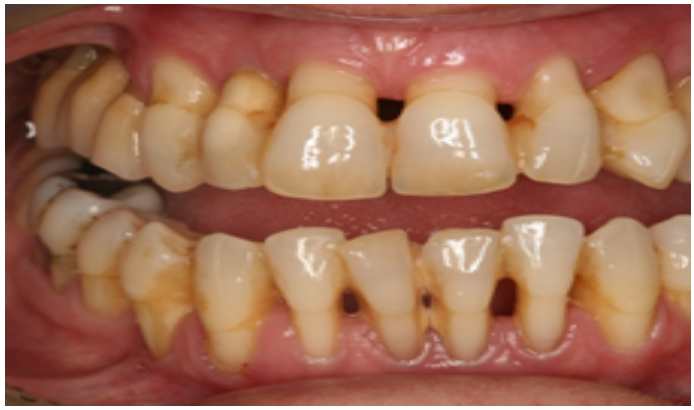

FIGURE 5: Alveolar boneresorption due to periodontitis.

Patophysiology of Periodontal Disease

This disease begins with a bacterial attack, then inflammatory cells will be stimulated to release free radicals to destroy these bacteria. Excessive free radicals can damage cells in the body. With an-tioxidants as one of the body's defense systems,

free radicals will be neutralized. The condition of the periodontium tissue is influenced by the internal antioxidants produced by the body to avoid oxidative stress, namely an imbalance of oxygen radicals and non-radicals that can damage cells by various mechanisms. (13)

One of the etiologies of periodontal disease is the presence of reactive oxygen species stimulated by bacterial antigens. (14) The main etiology of this disease is the gram negative facultative anaerobic bacteria which are present in the subgingival biofilm layer. These bacteria have the ability to activate the host defense mechanism in repairing damaged tissue but at the same time, these bacteria will produce toxins that will destroy the epithelium and periodontium structure. (15) When organisms are exposed to bacterial attack, it triggers an immune response between the bacterial pathogen and the host. These bacteria will cause the release of cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-αlpha (TNF-α), thereby increasing the number of leukocytes polymorphonuclear production. (16)

Leukocytes are the first cells that will fight pathogenic bacteria that attack the periodontium tissue. In the early stages of periodontitis, there is an increase in PMN which at the same time will increase the release of free radicals in the phagocytosis process against infection. Patients with periodontal disease have high levels of PMN and excessive ROS (reactive oxygen species) which will cause destruction of the gingival tissue, periodontal ligaments and alveolar bone in various ways including damaging DNA and stimulating the formation of proinflammatory cytokines. This also explains that the excessive involvement of ROS is related to tissue damage to the periodontium. (17)

The inflammatory process can cause tissue destruction of the periodontium. Initially, the PMN produced had a protective role against the periodontium tissue. However, the functionally activated PMN will show an increase in free radical production. Prostaglandin production also increases due to stimulation of gram-negative pathogenic bacteria. Enzymes such as collagenase, hyaluronidase and elastase also play a role in cell and periodontium tissue damage as a result of the working mechanism of these enzymes so that in this case it can be concluded that the immune system, phagocytosis and enzymes are factors that cause inflammation causing destruction of the periodontium tissu and cause tooth loss. (18)

3 | DISCUSSION

This disease begins with a bacterial attack, then inflammatory cells will be stimulated to release free radicals to destroy these bacteria. Excessive free radicals can damage cells in the body. With antioxidants as one of the body's defense systems, free radicals will be neutralized. The condition of the periodontium tissue is influenced by the internal antioxidants produced by the body to avoid oxidative stress, namely an imbalance of oxygen radicals and non-radicals that can damage cells by various mechanisms. (13)

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4 | CONCLUSIONS

Melatonin (N-acetyl-5-methoxytryptamine) is a hormone secreted by the pineal gland which will be synthesized by pinealocytes, then carry free tryptophan from the blood and convert tryptophan into serotonin. Melatonin in periodontitis patients acts as an anti-inflammatory and as an antioxidant so that it can eliminate free radicals in the body when there is inflammation in the periodontal tissue and also as an immunomodulator. In addition, melatonin also inhibits alveolar bone resorption and helps regenerate alveolar bone. Periodontitis patients show that the level of melatonin in their bodies has decreased when compared to melatonin levels in normal people. This proves that melatonin is needed in the process of inflammation and regeneration of alveolar bone which is absorbed due to periodontitis.

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